Recanalization Therapies in Acute Ischemic Stroke Patients

Impact of Prior Treatment With Novel Oral Anticoagulants on Bleeding Complications and Outcome

A Pilot Study

David J. Seiffge, MD; Robbert-JanVan Hooff, PhD; Christian H. Nolte, MD; Yannick Béjot, MD, PhD; Guillaume Turc, MD; Benno Ikenberg, MD; Eivind Berge, MD; Malte Persike, PhD; Nelly Dequatre-Ponchelle, MD; Daniel Strbian, MD PhD, MSc (Stroke Med); Waltraud Pfeilschifter, MD; Andrea Zini, MD; Arnstein Tveiten, PhD; Halvor Næss, MD, PhD; Patrik Michel, MD; Roman Sztajzel, MD; Andreas Luft, MD; Henrik Gensicke, MD; Christopher Traenka, MD; Lisa Hert, MD; Jan F. Scheitz, MD; Gian Marco De Marchis, MD; Leo H. Bonati, MD; Nils Peters, MD; Andreas Charidimou, MD, MSc, PhD; David J. Werring, PhD, FRCP; Frederick Palm, MD; Matthias Reinhard, MD; Wolf-Dirk Niesen, MD; Takehiko Nagao, MD; Alessandro Pezzini, MD; Valeria Caso, MD; Paul J. Nederkoorn, MD; Georg Kägi, MD; Alexander von Hessling, MD; Visnja Padjen, MD; Charlotte Cordonnier, MD; Hebun Erdur, Philippe A. Lyrer, MD; Raf Brouns, PhD; Thorsten Steiner, MD; Turgut Tatlisumak, MD; Stefan T. Engelter, MD; for the NOACISP Study Group*

Background—We explored the safety of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) in patients with ischemic stroke on non-vitamin K antagonist oral anticoagulants (NOACs, last intake <48 hours) in comparison with patients (1) taking vitamin K antagonists (VKAs) or (2) without previous anticoagulation (no-OAC).

Methods and Results—This is a multicenter cohort pilot study. Primary outcome measures were (1) occurrence of intracranial hemorrhage (ICH) in 3 categories: any ICH (ICH_{any}), symptomatic ICH according to the criteria of the European Cooperative Acute Stroke Study II (ECASS-II) ($sICH_{ECASS-II}$) and the National Institute of Neurological Disorders and Stroke (NINDS) thrombolysis trial ($sICH_{NINDS}$); and (2) death (at 3 months). Cohorts were compared by using propensity score matching. Our NOAC cohort comprised 78 patients treated with IVT/IAT and the comparison groups of 441 VKA patients and 8938 no-OAC patients. The median time from last NOAC intake to IVT/IAT was 13 hours (interquartile range, 8–22 hours). In VKA patients, median pre-IVT/IAT international normalized ratio was 1.3 (interquartile range, 1.1–1.6). ICH_{any} was observed in 18.4% NOAC patients versus 26.8% in VKA patients and 17.4%

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From Stroke Center and Neurology, University Hospital Basel, Switzerland (D.J.S., H.G., C.T., L.H., G.M.D.M., L.H.B., N.P., P.A.L., S.T.E.); Department of Neurology, Universitair Ziekenhuis Brussel and Center for Neurosciences (C4N), Vrije Universiteit Brussel (VUB), Belgium (R.-J.V.H., R.B.); Department of Neurology and Center for Stroke Research Charité, Berlin, Germany (C.H.N., J.F.S., H.E.); Department of Neurology, University Hospital, Dijon, France (Y.B.); Department of Neurology, Sainte-Anne Hospital, Paris, France (G.T.); Department of Neurology, Frankfurt Höchst Hospital, Germany (B.I., T.S.); Department of Internal Medicine, Oslo University Hospital, Norway (E.B.); Department of Statistical Methods, Gutenberg University, Mainz, Germany (M.P.); Department of Neurology, University Hospital, Lille, France (N.D.-P., C.C.); Department of Neurology, Helsinki University Central Hospital, Finland (D.S., T.T.); Department of Neurology, University Hospital, Frankfurt am Main, Germany (W.P.); Stroke Unit, Department of Neuroscience, S'Agostino-Estense Hospital, AUSL Modena, Italy (A.Z.); Department of Neurology, Sorlandet Sykehus Kristiansand, Norway (A.T.); Department of Neurology and Centre for Neurovascular Diseases, Haukeland University Hospital, Bergen, Norway (H.N.); Department of Neurology, University Hospital Lausanne, Switzerland (P.M.); Department of Neurology, University Hospital of Geneva and Medical School, Switzerland (R.S.); Department of Neurology, University Hospital Zurich, Switzerland (A.L.); Stroke Research Group, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom (A.C., D.J.W.); Department of Neurology, Municipal Hospital, Ludwigshafen, Germany (F.P.); Department of Neurology, University Hospital Freiburg, Germany (M.R., W.-D.N.); Department of Neurology, Tokyo Women's Medical University Hospital, Japan (T.N.); Department of Clinical and Experimental Sciences, Neurology Clinic, University of Brescia, Italy (A.P.); Department of Neurology, Perugia, Italy (V.C.); Academic Medical Center, University of Amsterdam, The Netherlands (P.N.); Department of Neurology, Kantonsspital St. Gallen, Switzerland (G.K.); Department of Neuroradiology, University Hospital Basel, Switzerland (A.v.H.); Neurology Clinic, Clinical Centre of Serbia, Belgrad (V.P.); University Hospital, Heidelberg, Germany (T.S.); Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden (T.T.); Department of Neurology, Sahlgrenska University Hospital, Gothenburg, Sweden (T.T.); and Neurorehabilitation Unit, University and University Center for Medicine of Aging and Rehabilitation Basel, Felix Platter Hospital, Basel, Switzerland (S.T.E.).

*A complete list of the NOACISP Study Group can be found in the online-only Data Supplement.

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Correspondence to David J. Seiffge, MD, Department of Neurology and Stroke Center, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. E-mail david.seiffge@usb.ch

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in no-OAC patients. $sICH_{ECASS-II}$ and $sICH_{NINDS}$ occurred in 2.6%/3.9% NOAC patients, in comparison with 6.5%/9.3% of VKA patients and 5.0%/7.2% of no-OAC patients, respectively. At 3 months, 23.0% of NOAC patients in comparison with 26.9% of VKA patients and 13.9% of no-OAC patients had died. Propensity score matching revealed no statistically significant differences.

Conclusions—IVT/IAT in selected patients with ischemic stroke under NOAC treatment has a safety profile similar to both IVT/IAT in patients on subtherapeutic VKA treatment or in those without previous anticoagulation. However, further prospective studies are needed, including the impact of specific coagulation tests. **(*Circulation*. 2015;132:1261-1269. DOI: 10.1161/CIRCULATIONAHA.115.015484.)**

Key Words: anticoagulants ■ endovascular procedures ■ intra-arterial treatment ■ intracranial hemorrhages ■ ischemic stroke ■ non-vitamin K antagonist oral anticoagulants ■ thrombolytic therapy ■ vitamin K antagonists

Atrial fibrillation is a major risk factors for ischemic stroke.[1] Non-vitamin K antagonist oral anticoagulants (NOACs) are at least as effective as vitamin K antagonists (VKAs) in preventing ischemic stroke in patients with atrial fibrillation (AF), with a better safety profile, especially for intracranial bleeding.[2–4] NOACs directly target selected players in the coagulation cascade as the direct thrombin inhibitor dabigatran or the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban.[2,5] Therefore, onset of the anticoagulatory effect of NOACs is quick (peak levels between 2 and 5 hours after intake). Anticoagulative effects of NOACs last only for several hours to a few days, whereas treatment with VKA results in a slow-onset and sustained, long-lasting inhibition of the coagulation cascade.[6]

Clinical Perspective on p 1269

One percent to 2% of all individuals have AF, a proportion that will increase as populations age and diagnostic procedures improve. Despite the best medical treatment with VKA or NOAC, 1.11% to 3.24% of patients with AF will have an ischemic stroke annually.[2] Furthermore, patients taking VKAs or NOACs for reasons other than AF can develop a stroke. Many of these patients will be evaluated at emergency departments for eligibility for acute recanalization therapies. For patients with ischemic stroke despite VKA, there are both guidelines[7] and registry-based observational data[8,9] indicating that the use of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) can be safe under certain conditions.

However, it remains uncertain how patients with ischemic stroke while taking NOACs should be treated. Current guidelines consider IVT contraindicated and mention the cautious use of IAT.[7] Withholding acute recanalization therapies from all patients with acute stroke under NOAC treatment would deny an effective treatment to a substantial number of patients with stroke.

Theoretical approaches to guide the use of IVT or IAT in patients with stroke taking NOACs have been published.[10–13] Furthermore, a few case reports on the use of IVT in patients taking dabigatran,[14–18] rivaroxaban,[19–22] or apixaban,[23] or IAT while taking dabigatran[24] reported favorable clinical outcomes. Conversely, 1 patient with ischemic stroke under dabigatran treatment had a fatal intracranial hemorrhage (ICH) associated with IVT.[25] Thus, currently, there is a lack of systematic outcome and safety data in patients with ischemic stroke under NOAC treatment at the time of IVT or IAT. Standardized data in large cohorts including any comparison group are not available. We therefore orchestrated a multicenter pilot project to investigate the safety of IVT and IAT for acute ischemic stroke in patients taking NOACs. Findings in NOAC patients were compared with (1) patients taking VKA and (2) patients without anticoagulation (no-OAC) before IVT/IAT in an observational cohort study.

Material and Methods

Study Design and Study Population

As a joint initiative of 25 stroke centers (see online-only Data Supplement for study group), we performed an observational collaborative cohort study to investigate: (1) the incidence of ICHs; and (2) functional outcome of patients with ischemic stroke occurring while taking NOACs who were treated with IVT or IAT or both (ie, bridging). IAT included intra-arterial thrombolysis, mechanical revascularization, or both. We introduced 2 comparison groups: first, patients with stroke who underwent IVT and IAT while taking VKA, and, second, patients without anticoagulation at the time of IVT/IAT.

All participating centers applied IVT/IAT according to well-established criteria and guidelines,[7,26] with the exception that, in selected patients, NOAC treatment was not considered an absolute exclusion criterion.

Each center reported on all NOAC patients treated with IVT/IAT during the period for which they had prospectively recorded data on consecutive patients treated with IVT/IAT in local registries or lists since approval of the first NOAC for stroke prevention in AF in their country up to December 31, 2014. Selected centers also provided information on all patients with stroke treated with IVT/IAT (1) while taking VKAs and (2) those without previous anticoagulation (no-OAC) based on local registries. For each contributing center, the number of patients, recruitment periods, and type of data source are summarized in Table I in the online-only Data Supplement.

Data Collection

Data for all patients were collected using a standardized form with predefined variables, as done in previous research.[27–29] Local investigators completed the forms systematically using data from (1) prospectively ascertained in-hospital thrombolysis or stroke registries or (2) from patients' records and charts in case patients were identified by local patient lists about consecutive IVT/IAT. Completed forms from all centers were sent to the coordinating center in Basel, where analyses of pooled data were performed.

Baseline Data

The following variables were used: age, sex, stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) score before IVT/IAT and at 24 hours, occlusion of main intracranial arteries (assessed by computed tomography angiography or magnetic resonance angiography), blood pressure, time-to-treatment, etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and the following risk factors applying

predefined criteria[27]: hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, history of previous ischemic stroke. Previous use of antiplatelets, antihypertensive drugs, and statins was assessed.[30] Laboratory measures before IVT/IAT included blood glucose levels, creatinine,[27] platelet count, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and calibrated anti–factor Xa assays for rivaroxaban, if available. Current use of VKAs or NOACs was recorded. In patients taking NOACs, agent and daily dosage, reason for use, last intake (in hours before IVT/IAT), and categorized reason for using IVT/IAT treatment were recorded. Functional 3-month outcome was assessed by outpatient visits or telephone interviews by using the modified Rankin Scale (mRS).

Outcome Measures

Primary outcome measures were the occurrence of ICH in 3 categories, or death within 3 months (ie, mRS of 6, denoted as mRS_6). ICH included: (1) any ICH on follow-up imaging including hemorrhagic transformation (ICH_{any}); (2) symptomatic ICH (sICH) according to the criteria of the European Cooperative Acute Stroke Study II (ECASS-II) trial[31] ($sICH_{ECASS-II}$); and (3) sICH based on the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) thrombolysis trial[32] ($sICH_{NINDS}$).

Secondary outcome measures were: (1) NIHSS at 24 hours; (2) major neurological improvement, defined as an improvement in NIHSS score of 8 points at 24 hours in comparison with the initial NIHSS (or an NIHSS score of 0 at 24 hours) as defined in previous research[33]; and (3) favorable 3-month outcome (ie, mRS of 0, 1, or 2, denoted as mRS_{0-2}).

Statistical Analyses

We used a bootstrapping procedure[34] that combined propensity score matching[35] with multiple imputation.[36] Because of the heterogeneous sample sizes between groups, we used triple group (TriMatch[37]) propensity score matching (PSM[38]) to balance characteristics of patients according to baseline covariates. Propensity scores were estimated from a logistic model and matched against a caliper of 0.25[39]. Variables likely to affect outcome or complications were chosen based on previous studies.[27–30] PSM predictors were age, sex, time-to-treatment, admission NIHSS, systolic and diastolic blood pressure, blood glucose level, creatinine and prior medication with statins, antihypertensive agents, or antiplatelets, as well, and the presence of diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, atrial fibrillation, and history of previous ischemic stroke.

Statistical analysis proceeded in 3 steps. First, missing data among the set of PSM predictors were completed by single imputation. Across all variables, 6.2% of data were missing (interquartile range [IQR], 0.6%–9.4%). Min/max of data missing for PSM were <0.1% [age]/0.3% [NIHSS on admission] and 15.9% [creatinine on admission]. Note that outcome variables were not imputed, but patients with missing values were dropped from analysis. Second, propensity scores were estimated and patients in the NOAC, VKA, and no-OAC groups were matched based on their propensity scores. Third, statistical analyses were performed on the matched sample and test statistics retained. Overall differences in NIHSS at 24 hours were analyzed with univariate analysis of variance with treatment group as the between-subjects factor. Pairwise comparisons between treatment groups were computed as a priori contrasts. Overall differences in the proportion of patients with ICH_{any}, major neurological improvement, mRS_{0-2}, and mRS_6 were tested with χ^2 tests. Pairwise differences between treatment groups for ICH_{any}, major neurological improvement, mRS_{0-2}, and mRS_6 were assessed with 2-sample binomial tests. Pairwise differences for $sICH_{NINDS}$ and $sICH_{ECASS-II}$ were tested by using the Fisher exact test. Overall differences for $sICH_{ECASS-II}$ and $sICH_{NINDS}$ could not be evaluated owing to very low incident rates in the NOAC group. Only pairwise Fisher exact tests were computed. Odds ratios and their 95% confidence intervals are provided for all instances of statistical significance. This procedure was repeated 50 000 times to gain a reliable bootstrap estimation of the empirical distribution of test statistics and *P* values.

Statistical analyses were performed by using R for Windows, version 3.1.2. All tests were 2-tailed, and statistical significance was determined at the α-level of 0.05. All pairwise tests used the Šidák correction for multiple comparisons,[40] yielding $\alpha' = 0.003$.

Subgroup Analyses

First, patients treated with IVT only (ie, excluding those with IAT only) were analyzed by comparing all groups. Second, in NOAC patients, all patients with IVT/IAT decisions based on the findings of the calibrated anti–factor Xa assays were descriptively analyzed. Third, we applied a post hoc comparison of NOAC patients with VKA patients stratified to the INR in 2 strata: VKA with INR >1.7 and with INR ≤1.7. For all subgroup analysis, we performed descriptive analyses only, owing to the small numbers.

Ethics

The study was approved by the ethics committee in Basel, Switzerland. The requirement for additional local ethical approval differed among participating centers and was acquired as necessary.

Results

Study Population

Our patient cohort included 9457 patients with acute ischemic stroke treated with IVT or IAT. The NOAC cohort comprised 78 patients (apixaban n=2, dabigatran n=29, and rivaroxaban n=47). IVT was used in 51 NOAC patients, including 6 who received IVT followed by IAT. IAT only was used in 27 NOAC patients; 25 of these 27 patients underwent purely mechanical thrombectomy. The comparison groups comprised (1) 441 VKA (phenprocoumon or acenocoumarol in all centers except Helsinki/Finland: warfarin) patients and (2) 8938 patients that were not on anticoagulation when they received IVT or IAT (no-OAC; Table I in the online-only Data Supplement).

Baseline Characteristics

There were significant differences in baseline characteristics between all cohorts. Baseline characteristics and the recanalization therapies applied are displayed in Table 1 (before PSM) and Table 2 (after PSM).

Last Intake, Coagulation Parameters, and Indication for NOAC Treatment

For NOAC patients, the median time between last intake and IVT/IAT was 13 hours (IQR, 8–22 hours); it was ≤12 hours in 38 patients, 13 to 24 hours in 30 patients, 25 to 48 hours in 7 patients; and unknown (but within <48 hours) in 3 patients. Atrial fibrillation was the indication for NOAC use in 69 of 78 (88%) patients. Other indications included prevention (n=2) and treatment (n=3) of deep vein thrombosis and other/not recorded (n=4).

In patients receiving rivaroxaban (n=47), the median INR was 1.3 (IQR, 1.1–1.51) and the mean aPTT was 32 (IQR, 27–35) seconds; in patients receiving dabigatran (n=29), median INR was 1.3 (IQR,1.1–1.5) and mean aPTT was 32 (IQR, 27–35) seconds. The 2 apixaban patients had INRs of 1.18 and 1.16 and aPTTs of 32 and 33 seconds, respectively.

In the VKA group, the median INR was 1.3 (IQR, 1.1–1.58). In 308 VKA patients (69.8%), the INR was ≤1.7. In 80 VKA patients (18.1%), no INR was recorded. Among the 53 VKA patients (12%) with INR >1.7 (median, 2.0 [IQR, 1.9–2.35]), 37 were treated with IVT, whereas 16 had IAT (median INR, 2.15[IQR, 2.0–2.87]).

Table 1. Baseline Characteristics (Before Matching)

	Novel Oral Anticoagulants	Vitamin K Antagonists	no-OAC	Statistics
	(n=78)	(n=441)	(n=8938)	*P* Value
Age, y, median (IQR)	76 (68–81)	77 (68–83)	71 (60–79)	< 0.001*
Female sex, n (%)	36 (49.3)	201 (45.6)	3915 (43.9)	0.50†
Time-to-treatment, min, median (IQR)	174.5 (115.5–240)	140 (90–185)	126 (80–175)	<0.001*
NIHSS score, median (IQR)	14.5 (7–19)	14 (8–19)	10 (6–16)	<0.001*
INR, median (IQR)	1.14 (1.06–1.3)	1.3 (1.1–1.6)	1 (1–1.1)	<0.001*
Occlusion of intracranial artery, n (%)	50 (75.8)	174 (68.5)	2070 (46.7)	< 0.001†
Systolic blood pressure, mm Hg, mean (IQR)	148 (127.5–164.5)	151.5 (132–170)	154 (139–170)	0.15*
Diastolic blood pressure, mm Hg, mean (IQR)	80 (67–93.5)	83 (73–94)	83 (74–94)	0.18*
Type of acute recanalization therapy‡				
IV thrombolysis only, n (%)	45 (57.7)	354 (84.9)	7788 (93.2)	
IV thrombolysis and IA treatment, n (%)	6 (7.69)	36 (8.63)	521 (6.24)	
IA treatment only, n (%)	27 (34.62)	27 (6.47)	43 (0.51)	
Concomitant treatment				
Previous use of statins, n (%)	27 (39.1)	160 (38)	1954 (25.5)	<0.001†
Previous use of antihypertensive drugs, n (%)	61 (87.1)	346 (82.2)	4424 (54.4)	<0.001†
Previous treatment with antiplatelets, n (%)	14 (18.2)	64 (14.8)	3008 (35.8)	<0.001†
Risk factors				
Atrial fibrillation, n (%)	68 (87.2)	345 (78.8)	2152 (24.3)	<0.001†
Diabetes mellitus, n (%)	17 (24.3)	98 (22.2)	1500 (16.8)	0.07†
Hypertension, n (%)	61 (87.1)	349 (79.1)	5627 (63.2)	<0.001†
Hypercholesterolemia, n (%)	32 (49.2)	184 (42.5)	3559 (41.4)	0.45†
Coronary artery disease, n (%)	24 (34.3)	107 (25.4)	1371 (16.9)	<0.001†
History of stroke, n (%)	18 (25.4)	110 (25.4)	1211 (14)	<0.001†
Stroke cause‡				
Cardioembolic, n (%)	64 (85.3)	224 (61.4)	2623 (33.1)	
Large artery atherosclerosis, n (%)	2 (2.7)	97 (26.6)	2003 (25.3)	
Small artery occlusion, n (%)	0 (0)	3 (0.82)	574 (7.25)	
Other, n (%)	1 (1.33)	11 (3.01)	338 (4.27)	
>1 or undetermined, n (%)	8 (10.67)	29 (7.95)	2233 (28.21)	

IA indicates intra-arterial; INR, international normalized ratio; IQR, interquartile rate; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and no-OAC, without previous anticoagulation.

*Kruskal-Wallis test with *df*=2

†χ^2 test with *df*=2

‡No test computed (small sample sizes).

The reported decision to use IVT/IAT in NOAC patients was based on the time since last intake >24 hours (n=10), low levels in drug-specific coagulation assays (n=23), normal values in routine coagulation assays (n=10), or on other/unknown reasons (n=35). The latter included patients in which the use of NOAC was not known before IVT/AT treatment but discovered thereafter.

Outcome Measures

Outcome measure statistics are displayed in Table 3 (before PSM) and Table 4 (after PSM).

Primary Outcome Measures

ICH_{any} was observed in 14 of 76 (18.4%) NOAC patients in comparison with 105 of 394 (26.6%) VKA patients, and 1332 of 7677 (17.4%) patients in the no-OAC group (*P*=0.30). $sICH_{ECASS\text{-}II}$ occurred in 2 of 76 (2.6%) NOAC patients in comparison with 27 of 415 (6.5%) VKA patients and 417 of 8281 (5.0%) no-OAC patients (*P*=0.48). $sICH_{NINDS}$ was reported for 3 of 76 (3.9%) NOAC patients, 40 of 432 (9.3%) VKA patients, and 616 of 8539 (7.2%) no-OAC patients (*P*=0.56). At 3 months, 17 of 74 (23.0%) NOAC patients had died in comparison with 113 of 420 (26.9%) VKA patients and 1172 of 8414 (13.9%) no-OAC patients (*P*=0.44).

Secondary Outcome Measures

A favorable 3-month outcome occurred in 30 of 74 (40.5%) NOAC patients in comparison with 166 of 420 (39.5%) VKA patients and 4736 of 8414 (56.3%) no-OAC patients. Here, we find the only significant overall difference of frequencies in our data (*P*=0.037). The pattern of frequencies suggests a more favorable 3-month outcome for no-OAC patients than for the VKA and the NOAC patients. Pairwise comparisons, however, remain insignificant in all cases (all *P*>0.05). Major neurological improvement occurred similarly often in all 3 groups.

Table 2. Baseline Characteristics After Propensity Score Matching

	Novel Oral Anticoagulants (n=63)	Vitamin K Antagonists (n=339)	no-OAC (n=210)
Age, y, median (IQR)	76 (64–81)	77 (68–83)	75 (67–81)
Female sex, n (%)	28 (45)	158 (46.6)	108 (51.5)
Time-to-treatment, min, median (IQR)	176 (117–242)	141 (93–180)	132 (90–176)
NIHSS score, median (IQR)	15 (7–19)	14 (8–19)	14 (8–19)
INR, median (IQR)	1.14 (1.07–1.3)	1.3 (1.1–1.59)	1.05 (1–1.12)
Occlusion of intracranial artery, n (%)	45 (76.6)	150 (70)	59 (54.5)
Systolic blood pressure, mm Hg, mean (IQR)	148 (128–165)	151 (131–170)	151 (135–168)
Diastolic blood pressure, mm Hg, mean (IQR)	80 (68–93)	83 (73–93)	81 (72–93)
Type of acute recanalization therapy			
IV thrombolysis only, n (%)	34 (53.5)	287 (84.8)	196 (93.2)
IV thrombolysis and IA treatment, n (%)	4 (6.3)	29 (8.7)	13 (6.1)
IA treatment only, n (%)	25 (40.2)	22 (6.5)	1 (0.7)
Concomitant treatment			
Previous use of statins, n (%)	25 (40)	112 (34.1)	71 (35.9)
Previous use of antihypertensive drugs, n (%)	56 (88.9)	275 (82.4)	180 (87.2)
Previous treatment with antiplatelets, n (%))	13 (19.9)	49 (14.6)	51 (24.5)
Risk factors			
Atrial fibrillation, n (%)	54 (86)	265 (78.2)	176 (84.1)
Diabetes mellitus, n (%)	16 (24.7)	68 (20.1)	50 (23.9)
Hypertension, n (%)	55 (87.5)	269 (79.3)	173 (82.6)
Hypercholesterolemia, n (%)	31 (52.6)	146 (43)	98 (47.2)
Coronary artery disease, n (%)	21 (32.6)	80 (24.3)	62 (29.8)
History of stroke, n (%)	15 (24.1)	61 (18.2)	45 (21.3)
Stroke cause			
Cardioembolic, n (%)	50 (82.1)	171 (59)	105 (53)
Large artery atherosclerosis, n (%)	2 (3.3)	83 (28.8)	68 (34.1)
Small artery occlusion, n (%)	0 (0)	2 (0.8)	3 (1.6)
Other, n (%)	1 (1.7)	10 (3.4)	2 (0.9)
>1 or undetermined, n (%)	8 (13)	23 (8)	21 (10.4)

IA indicates intra-arterial; INR, international normalized ratio; IA, intra-arterial; IQR, interquartile rate; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and no-OAC, without previous anticoagulation.

Subgroup Analyses

IVT Only

IVT only was used in 51 NOAC and 390 VKA patients. ICH_{any} occurred in 8 (15.7%) patients on NOAC and 54 (28.7%) patients on VKA. $sICH_{ECASS-II}$ and $sICH_{NINDS}$ occurred in 2 (4.0%) patients on NOAC each, in comparison with 7 (3.6%) and 11 (5.7%) patients on VKA.

IVT/IAT and Calibrated Anti–Factor Xa Assays

In 21 patients taking rivaroxaban, the decision to administer IVT was based on calibrated anti-factor Xa assays with a mean level of 21ng/mL (IQR, 8–23 ng/mL). In all these patients anti–factor Xa levels were <100 ng/mL. Each of the 3 patients with anti–factor Xa levels of >100ng/mL (range, 146–246 ng/mL) had IAT only. None of these patients experienced a sICH.

NOAC and $VKA_{INR>1.7}$ or $VKA_{INR\leq 1.7}$

Outcome measures for the subgroup analysis comparing patients on NOAC and $VKA_{INR>1.7}$ or $VKA_{INR}\leq_{1.7}$ are summarized in Table 5.

Discussion

This observational multicenter pilot study yielded the following key findings: first, in selected patients with ischemic stroke who are on NOAC treatment (last intake ≤48 hours), IVT/IAT was feasible and not associated with an excessive risk of ICH in comparison with patients on VKA or without oral anticoagulation. Second, in comparison with VKA patients, NOAC patients had numerically fewer intracranial hemorrhages, lower death rates, and a better functional outcome. However, none of these differences reached statistical significance.

Overall, our study highlights that, at least in experienced stroke centers, IVT/IAT application in carefully selected patients with ischemic stroke under NOAC treatment did not raise any suggestion of safety concerns.

The percentage of $sICH_{ECASS-II}$ (2.6%) or $sICH_{NINDS}$ (3.9%) in our NOAC cohort was comparable to sICH rates in a recent multicenter observational study (4.7%)[41] or in ECASS-3 (5.3%).[42] This finding might not be necessarily reassuring, because the upper limit of the 95%CI (ie, 6.13% for

Table 3. Primary and Secondary Outcome Measures Before Matching

	Novel Oral Anticoagulants	Vitamin K Antagonists	no-OAC	Statistics
	(n=78)	(n=441)	(n=8938)	p
Primary outcome				
ICH_{any}	14 of 76 (18.4%)	105 of 394 (26.6%)	1332 of 7677 (17.4%)	<0.001
$sICH_{ECASS-II}$	2 of 76 (2.6%)	27 of 415 (6.5%)	417 of 8281 (5.0%)	.25*
$sICH_{NINDS}$	3 of 76 (3.9%)	40 of 432 (9.3%)	616 of 8539 (7.2%)	.15
Death at 3 mo (mRS_6)	17 of 74 (23.0%)	113 of 420 (26.9%)	1172 of 8414 (13.9%)	<0.001
Secondary outcome				
NIHSS at 24 h, median (IQR)	9 (2–14)	8 (3–16)	5 (2–13)	<0.001
Major neurological improvement*	24 of 77 (31.2%)	128 of 405 (31.6%)	1958 of 6834 (28.7%)	.40
Favorable clinical outcome at 3 mo (mRS_{0-2})	30 of 74 (40.5%)	166 of 420 (39.5%)	4736 of 8414 (56.3%)	<0.001

ECASS-II indicates European Cooperative Acute Stroke Study II; ICH, intracranial haemorrhage; ICH_{any}, any intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; no-OAC, without previous anticoagulation; sICH, symptomatic intracranial hemorrhage $sICH_{ECASS-II}$, any ICH with neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death; and $sICH_{NINDS}$, any ICH on follow-up imaging with any decline in neurological status.

* Major neurological improvement – improvement in NIHSS score of 8 points at 24 h compared to initial NIHSS (or NIHSS score of 0 at 24 h)

$sICH_{ECASS-II}$ and 8.2%for ICH_{NINDS}, respectively) indicates that the sICH risk might still be higher than reported in literature for patients without anticoagulation. Based on the observation that the ICH risk in all categories was numerically lower in NOAC than in VKA patients, this scenario seems unlikely, taking into account that IVT/IAT in VKA patients has been reported safe under certain conditions.[8,9] Reasons for the relative safety of IVT/IAT under NOAC may include the lower baseline risk of ICH of NOACs in patients with stroke.[3]

The decision to use IVT was based on rivaroxaban concentration levels in the calibrated anti–factor Xa assay in 22 of our patients and 2 recent single cases.[19,21] All 24 IVT-treated patients had levels of the calibrated anti–factor Xa assay <100ng/mL. None had sICH but 1 of 24 had an asymptomatic ICH. This threshold, recommended previously based on theoretical and pharmacological considerations and data,[11] may indeed serve as a clinically useful tool to select patients. However, because of the small sample size, further research about the clinical meaning of NOAC-concentration thresholds is needed.

Our analysis had the following strengths: (1) We report on a multicenter cohort; (2) data ascertainment was undertaken systematically and included 2 comparison groups; and (3) safety issues, and functional outcome, as well, were addressed.

Table 4. Primary and Secondary Outcome Measures After Propensity Score Matching

	Novel Oral Anticoagulants	Vitamin K Antagonists	no-OAC	Statistics
	(n=63)	(n=339)	(n=210)	*P* Value
Primary outcome				
ICH_{any}	13 of 62 (20.8%)	85 of 300 (28.4%)	44 of 184 (23.8%)	0.30
$sICH_{ECASS-II}$	2 of 62 (3.2%)	21 of 338 (6.1%)	14 of 207 (6.6%)	0.48*
$sICH_{NINDS}$	3 of 62 (4.8%)	30 of 338 (8.9%)	19 of 203 (9.6%)	0.56*
Death at 3 mo (mRS_6)	16 of 60 (26.1%)	76 of 324 (23.6%)	43 of 204 (20.9%)	0.44
Secondary outcome				
NIHSS at 24 h, median (IQR)	10 (2–15)	8 (3–16)	8 (3–17)	0.45
Major neurological improvement†	20 of 62 (31.4%)	98 of 317 (30.8%)	41 of 154 (26.3%)	0.29
Favorable clinical outcome at 3 mo (mRS_{0-2})	23 of 60 (39%)	138 of 324 (42.7%)	88 of 204 (43.2%)	0.03‡

ECASS-II indicates European Cooperative Acute Stroke Study II; ICH, intracranial haemorrhage; ICH_{any}, any intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; no-OAC, without previous anticoagulation; sICH, symptomatic intracranial hemorrhage; $sICH_{ECASS-II}$, any ICH with neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death; and $sICH_{NINDS}$, any ICH on follow-up imaging with any decline in neurological status.

*χ^2 approximation unstable (small group sizes).

†Major neurological improvement – improvement in NIHSS score of 8 points at 24 h compared to initial NIHSS (or NIHSS score of 0 at 24 h).

‡All pairwise comparison: $P>0.05$.

Table 5. Outcome Measures Stratified to VKA With INR Subgroups Versus NOAC Patients

	Vitamin K Antagonists		Novel Oral Anticoagulants
	INR >1.7	INR ≤1.7	
	(n=135)	(n=306)	(n=78)
Primary outcome			
ICH_{any}	36 of 123 (29.27%)	69 of 271 (25.46%)	14 of 76 (18.42%)
$sICH_{ECASS-II}$	13 of 116 (11.21%)	14 of 299 (4.68%)	2 of 76 (2.63%)
$sICH_{NINDS}$	16 of 135 (11.85%)	24 of 297 (8.08%)	3 of 76 (3.95%)
Death at 3 mo (mRS_6)	38 of 129 (29.46%)	75 of 291 (25.77%)	17 of 74 (22.97%)
Secondary outcome			
NIHSS at 24 h, median (IQR)	9 (3–17)	8 (3–16)	9 (2–14)
Major neurological improvement	42 of 123 (34.15%)	86 of 282 (30.50%)	24 of 77 (31.17%)
Favorable clinical 3-mo outcome (mRS_{0-2})	57 of 129 (44.19%)	109 of 291 (37.46%)	30 of 74 (40.54%)

ECASS-II indicates European Cooperative Acute Stroke Study II; ICH, intracranial haemorrhage; ICH_{any}, any intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; sICH, symptomatic intracranial hemorrhage; $sICH_{ECASS-II}$, any ICH with neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death; and $sICH_{NINDS}$, any ICH on follow-up imaging with any decline in neurological status.

Nevertheless, several limitations should be noted: First, this is a retrospective study. Second, there was heterogeneity between centers with regard to the criteria applied for the decision to use or avoid IVT/IAT in individual patients, and whether IVT or IAT was preferred. Third, NOAC patients differed from the VKA and the no-OAC patients in several baseline characteristics. Despite application of PSM as an effort to minimize confounding effects, unmeasured characteristics might have differed between these patients and confounded our results. Fourth, a comparison group of patients with stroke despite NOAC treatment not treated with IVT/IAT was not available. Thus, the bleeding risk in patients with ischemic stroke taking NOACs treated with IVT/IAT versus those without IVT/IAT could not be studied. Fifth, despite being the largest cohort available so far, the total numbers of patients taking NOACs or VKAs are still relatively small. Thus, subgroup analyses were performed descriptively. Accordingly, we stress the exploratory character of our study and urge a cautious interpretation of our findings.

The safety of IVT in patients on VKA and an INR ≤1.7 has been established based on large cohorts.[8,9] The knowledge about IVT in NOAC patients is limited and based on case reports.[14–18,20,21,24] Data from animal models showed no excessive risk of ICH after IVT in rodents with a prior treatment with rivaroxaban,[43,44] dabigatran,[45,46] and apixaban[44] in comparison with VKA. Currently, the use of IVT for acute ischemic stroke in patients with a recent (<48 hours) intake of a NOAC is regarded off-label.[7] A recent survey among US vascular neurologists showed a lack of consensus regarding the management of patients with ischemic stroke on dabigatran.[47] The guidelines of the American Heart Association/American Stroke Association state that IVT might be considered "[if] sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function)."[7] NOACs have only limited influence on standard coagulation assays.[48] Practical approaches for the use of IVT/IAT in patients with stroke taking NOACs have been proposed.[10,11] A recently developed and prospectively assessed approach for patients with stroke despite dabigatran by using aPTT and thrombin time reported on 2 patients receiving IVT within 8 months of recruitment. Neither had ICH.[49]

Twenty-seven of our NOAC patients were treated with IAT only; 25 of those had pure mechanical thrombectomy. sICH was absent in all patients and also in a case report of mechanical thrombectomy under NOAC.[24] Despite the small numbers, the absence of sICH suggests, that in patients with abnormal hemostasis and NOAC treatment, mechanical recanalization strategies might be more appropriate. However, it remains to be shown, whether sICH rates are indeed lower when NOAC patients with acute stroke are treated with mechanical IAT than with IVT. For patients with abnormal hemostasis[50,51] and treatment with IAT, sICH rates were 7.1%[50] and 11.4%,[51] which were numerically higher than those observed in our NOAC cohort treated with IVT.

In conclusion, our data suggest that IVT/IAT treatment in patients with an ischemic stroke despite NOAC is feasible and probably not associated with an excessive risk for ICH. However, this assumption requires that patients (1) are treated in experienced stroke centers and (2) are carefully selected based on time from last intake of the oral anticoagulant and the findings of specific coagulation tests. Nevertheless, our observations must be considered with caution before generalizing them to standard practice. More research is needed, which should include a systematic assessment of the clinical meaning of coagulation tests and drug doses with regard to safety and effectiveness measures. We recently set up a prospective multicenter registry to systematically investigate the management of patients experiencing an acute ischemic stroke or intracranial hemorrhage while taking NOACs (NOACISP-ACUTE, cinicaltrials.gov: NCT02353585).

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CLINICAL PERSPECTIVES

Non-vitamin K antagonist oral anticoagulants (NOACs) changed clinical practice and are now frequently used for stroke prevention in patients with atrial fibrillation. Despite their efficacy, patients with atrial fibrillation taking NOACs might experience an ischemic stroke. Clinical physicians are faced with the dilemma to evaluate patients on NOACs who present with ischemic stroke in stroke centers and to balance the risk of bleeding complications against benefits of recanalization therapies like intravenous thrombolysis (IVT) and intra-arterial treatment (IAT, including mechanical thrombectomy). This multicenter observational pilot study is the first to report on a cohort of patients with a previous recent (within the last 48 hours) intake of a NOAC treated with IVT/IAT for ischemic stroke and compares bleeding complications and outcome with a large data set of patients who were either on Vitamin K antagonists or without anticoagulation before IVT/IAT. In this study, in selected patients with ischemic stroke under NOAC treatment, IVT/IAT had a safety profile similar to both IVT/IAT in patients on subtherapeutic Vitamin K antagonist treatment or in those without previous anticoagulation. The present study suggests that IVT/IAT in patients with a previous intake of a NOAC might be safe and that specific clotting tests (eg, calibrated anti–factor Xa assays or hemoclot test) might be helpful to guide or support treatment decisions. Nevertheless, treatment with IVT/IAT in patients with a previous intake of a NOAC should be based on individual treatment decisions balancing the risks and benefits. It should be discussed with patients and next-of-kin. However, more data are needed and results from ongoing research studies are warranted (for example, NOACISP-ACUTE, cinicaltrials.gov: NCT02353585).

Recanalization Therapies in Acute Ischemic Stroke Patients: Impact of Prior Treatment With Novel Oral Anticoagulants on Bleeding Complications and Outcome

David J. Seiffge, Robbert-JanVan Hooff, Christian H. Nolte, Yannick Béjot, Guillaume Turc, Benno Ikenberg, Eivind Berge, Malte Persike, Nelly Dequatre-Ponchelle, Daniel Strbian, Waltraud Pfeilschifter, Andrea Zini, Arnstein Tveiten, Halvor Næss, Patrik Michel, Roman Sztajzel, Andreas Luft, Henrik Gensicke, Christopher Traenka, Lisa Hert, Jan F. Scheitz, Gian Marco De Marchis, Leo H. Bonati, Nils Peters, Andreas Charidimou, David J. Werring, Frederick Palm, Matthias Reinhard, Wolf-Dirk Niesen, Takehiko Nagao, Alessandro Pezzini, Valeria Caso, Paul J. Nederkoorn, Georg Kägi, Alexander von Hessling, Visnja Padjen, Charlotte Cordonnier, Hebun Erdur, Philippe A. Lyrer, Raf Brouns, Thorsten Steiner, Turgut Tatlisumak and Stefan T. Engelter
for the NOACISP Study Group*

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SUPPLEMENTAL MATERIAL

Novel oral anticoagulants in stroke patients (NOACISP) Study Group*

Belgium: R-J Van Hooff and R. Brouns, Department of Neurology, University Hospital, Center for Neurosciences (C4N), Brussels;
France: Y. Béjot and M Giroud, Department of Neurology, University Hospital, Dijon; C. Cordonnier, D. Leys, M. Ferrigno and N. Dequatre-Ponchelle, Department of Neurology, University Hospital, Lille; G. Turc and J.L. Mas, Department of Neurology, Sainte-Anne Hospital, Paris; C. Oppenheim and O. Naggara, Department of Neuroradiology, Sainte-Anne Hospital, Paris
Finland: D. Strbian and T. Tatlisumak, Department of Neurology, University Central Hospital, Helsinki;
Germany: H. Erdur and Ch. Nolte, Department of Neurology and Center for Stroke Research Charité, Berlin; A. Grau and F. Palm, Department of Neurology, Municipal Hospital Ludwigshafen, W. Pfeilschifter, Department of Neurology, University Hospital, Frankfurt am Main; B. Ikenberg and Th. Steiner, Department of Neurology, Frankfurt Höchst Hospital and University Hospital, Heidelberg; M Reinhard and WD Niessen, Department of Neurology, University Hospital, Freiburg
Italy: A. Zini, Stroke Unit, Department of Neuroscience, Nuovo Ospedale Civile, AUSL Modena, V. Caso, Department of Neurology, Perugia; A. Pezzini, University Hospital Brescia
R. Tanaka; Department of Neurology, Juntendo University Hospital, Tokyo. K. Kamiyama; Department of Neurosurgery, Nakamura Memorial Hospital, Hokkaido. Y. Watanabe; Department of Neurosurgery, Fukushima Red Cross Hospital, Fukushima.
The Netherlands: P. Nederkoorn and S. Zinkstok Academic Medical Center, University of Amsterdam
Norway: E. Berge and M. Jusofovic, Department of Internal Medicine, Oslo University Hospital; A. Tveiten, Department of Neurology, Sorlandet Sykehus, Kristiansand; H. Naess and L. Thomassen, Department of Neurology and Centre for Neurovascular Diseases, Haukeland University Hospital; Bergen
Switzerland: A. Eskandari and P. Michel, Department of Neurology, University Hospital Lausanne ;R. Stzajzel, Department of Neurology, University Hospital of Geneva and Medical School, Geneva; S. Wegener and A. Luft, Department of Neurology, University of Zurich; G. Kaegi, Department of Neurology, Kantonsspital St. Gallen; C. Traenka, H. Gensicke, GM De Marchis, L. Hert, L.H.. Bonati, N. Peters, P.A. Lyrer, D. Seiffge and S.T. Engelter, Stroke Center and Neurology, University Hospital Basel; Ch. Stippich and A. von Hessling, Department of Neuroradiology, University Hospital Basel
Serbia: V. Padjen School of Medicine, University of Belgrade
UK: A. Charidimou and D. J. Werring, Stroke Research Group, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London

*countries in alphabetic order

Supplemental Table 1. Participating centers, number of contributed patients receiving acute recanalization therapies and data source.

Center	Recanalization therapies in patents on NOAC	Recanalization therapies in patients on VKA	Recanalization therapies in patients without anticoagulation	Data source (registry or patient list*)
Belgium				
University Hospital Brussels	7	0	95	registry
France				
University Hospital, Dijon,	5	19	357	registry
Lille University Hospital	3	39	795	registry
Sainte-Anne Hospital, Paris	4	7	0	registry
Finland				
University Central Hospital, Helsinki	2	127	2482	registry
Germany				
Charité University Hospital Berlin,	11	34	877	registry
University Hospital Frankfurt	1	3	0	list
Frankfurt Höchst Hospital	3	0	0	list
University Hospital Freiburg	7	0	0	list
Municipal Hospital Ludwigshafen	0	8	136	registry
Italy				
University Hospital Modena	1	19	458	registry
University Hospital Perugia	1	0	0	registry
University Hospital Brescia	0	9	148	registry
Japan				
Tokyo Women's Medical University Hospital	10	0	0	registry
Netherlands				
Academic Medical Center, University of Amsterdam	0	7	585	registry

Norway				
Haukeland University Hospital	2	5	224	registry
Sorlandet Sykehus Kristiansand	1	0	404	registry
University Hospital Oslo	0	7	3	registry
Serbia				
University Hospital Belgrad	0	7	322	registry
Switzerland				
Centre Hospitalier Vaudois, Lausanne	2	80	781	registry
University Hospital Basel	14	56	899	registry
University Hospital Zürich#	1	3	46	registry
University Hospital, Geneva	1	0	0	registry
Kantonspital St. Gallen,	0	15	322	registry
United Kingdom				
University College London Hospitals NHS Foundation Trust London	2	0	0	list
Total	78	441	8938	

*Definition:

"Registry": In-hospital thrombolysis registry or stroke-registry of all consecutive patients receiving IVT/IAT with prospective ascertainment of all relevant data (at least vast majority).

"List": Lists of all consecutive stroke patients receiving IVT/IAT. Several individual patient data were derived from charts and/or records

recruitment period 04/2012-12/2013